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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/825,882
Filing Date: April 05, 2001
Appellant(s): ADLER, JON ELLIOT

Robin L. Teskin
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 11/15/04.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

A statement identifying the related appeals and interferences which will directly affect or be directly affected by or have a bearing on the decision in the pending appeal is contained in the brief.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is correct.

(6) Issues

The appellant's statement of the issues in the brief is correct, with the exception that it as at page 3, (not page 5), lines 11-12 of the advisory action wherein the examiner maintains that "it was impossible to predict that a particular T2R would bind a bitter tastant".

(7) Grouping of Claims

(I) The rejection of claims 158-185 under 35 U.S.C. § 101, stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(II) The rejection of claims 158-185 under 35 U.S.C. § 112 first paragraph, as the claimed invention is not supported by a substantial asserted utility, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation: the claims stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

Furthermore, claims 158, 159, 164-185 would stand or fall together on the issue of scope of enablement

(III) The rejection of claims 158, 159, 164-185 under 35 U.S.C. § 112 first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention: the claims stand or fall together because appellant's brief does not include a statement that this grouping of claims does not stand or fall together and reasons in support thereof. See 37 CFR 1.192(c)(7).

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Adler-E. et al., Cell 100(693-702)2000

Alexander et al., Proc. Natl. Acad. Sci. 89(3352-3356)1992

Bowie et al., 1990, Science 247:1306-1310

Brenner et al. PNAS 95(6073-6078)1998

Chandrashekar et al., Cell 100(703-711)2000

Guo-HH et al. PNAS 101(25)9205-9210, 2004

Hoon *et al., Cell* 96(541-551)1999

Horrobin, DF, British Med. Journal, 322(7280)239, July 2003.

Lahana R., Drug Discovery Today, 4(10)447-448, 1999

Lindemann, B. *Nature Neuroscience* 3(2)99-100, 2000

Perruccio and Kleinhaus, *Society Neurosc. Abs.* 26(1-2) Abstract No. 66.15, 2000

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

Claims 158-185 are rejected under 35 U.S.C. § 101, because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility, for the reasons of record, which are reiterated below.

The claims require that the polypeptide be a bitter taste receptor, yet the specification has not taught how to use this information in any particular way. The concept of "bitter taste" is known to involve multiple and as yet poorly characterized transduction schemes, see for example Perruccio and Kleinhaus, *Society for Neuroscience Abstracts* 26(1-2) Abstract No. 66.15, 2000. These transduction schemes are also thought to involve a large diversity of receptors – each receptor thought to bind specifically among a tremendous genus of structurally unrelated toxic or bitter tasting compounds, see the Abstract of Chandrashekar et al., Cell 100(703-711)2000 for example. The specification has given no indication as to which of these compounds is expected

to bind to and activate SEQ ID NO: 8. Without such knowledge, the artisan could not use the protein to manipulate any aspect of the senses involving taste. Instead, the specification has merely invited the skilled artisan to embark on a plan of research to try to find exactly what ligands to use and then to determine what the protein can be used for.

The claims are directed to polynucleotides of SEQ ID NO: 7 encoding a polypeptide of SEQ ID NO: 8 termed hT2R61, wherein the polypeptide is believed to be a component of a taste transduction pathway, particularly bitter taste transduction (page 8). The specification puts forth the instant hT2R61 is a member of the T2R family of taste-cell-specific GPCRs as described in Chandrashekar et al., Cell 100(703-711)2000; and that such family members are believed to involved in the taste detection of bitter substances but may be involved in other taste modalities as well, (see page 8, last full paragraph). The instant specification puts forth that the polypeptides are useful for "representing the perception of taste and/or for predicting the perception of taste in a mammal" (e.g. pg 67), although the specification does not appear to assert that the instant polypeptide mediates a response to any particular tastant or ligand. The specification suggests that the nucleic acids and the proteins they encode can be used as probes to dissect taste-induced behaviors (e.g. see page 6). Further, the specification indicates that the polypeptides can be used in a screening method to determine what molecules may activate or inhibit the polypeptides (see pages 9 and 50) and also to determine what the physiological effects of the polypeptides might be - the effects being those on "taste modulation". These proposed uses lack a substantial utility, because each of the proposed uses are of a general nature, and it would require undue experimentation on the part of the skilled artisan to determine what, particularly, the claimed polynucleotides could be used for.

A substantial utility is a practical use which amounts to more than a starting point for further research and investigation and does not require or constitute carrying out further research to identify or reasonably confirm what the practical use might ultimately be. For example, an assay that measures the presence of a material which has a stated correlation to a predisposition to the onset of a particular disease would be a practical use of the material. However, a method of modulating an unidentified aspect of what is collectively known as taste perception with an as yet unidentified material (e.g. agonists of the disclosed polypeptides) would not constitute a substantial utility. Basic research, such as studying the properties of the claimed product or the mechanisms in which the product is involved, does not constitute a substantial utility.

A stated belief that a correlation exists between the polypeptides and any of the collective phenomena that are encompassed by the concept of taste perception is not sufficient guidance to use the claimed polynucleotides to modulate any aspect of taste perception; it merely defines a starting point for further research and investigation and presents only an invitation to one of skill in the art to perform such further research and investigation. The molecular mechanisms of taste perception, are extremely complex and are known to use multiple transduction mechanisms. Even what could be thought of as a singular modality of taste perception, e.g. the perception of bitter taste, is not a single modality but a generalized response that is known to involve multiple and as yet poorly characterized transduction schemes, see for example Perruccio and Kleinhaus, *Society for Neuroscience Abstracts* 26(1-2) Abstract No. 66.15, 2000. Thus, the asserted uses of the polynucleotides as they relate to taste perception, are general and do not assert any particular use beyond an invitation to the skilled artisan to try to find a particular way in which the polynucleotides or polypeptides could be used.

Further, the asserted membership of the instant polypeptide in the family of T2R proteins described by Chandrashekar et al., (supra) does not, alone, impart a property to the polypeptide that could be exploited in such a way as to constitute a substantial utility. Chandrashekar et al. tested 11 different human T2R clones against a battery of different tastants and found only one clone that responded - and this response seems to be limited to only one tastant (see col 1 of page 707 and List of Tastants at page 710). Further, even this success seems to be rare in the art. Commenting on this family of receptors, other researchers have concluded that although T2R receptors have been suggested to be candidates for bitter taste receptors, "at present there is no functional evidence for this proposal", see Lindemann, B. *Nature Neuroscience* 3(2)99-100, 2000, last paragraph of column 2 of page 99. Appellant's disclosure simply offers an additional object for the skilled artisan to examine. Although Appellant's disclosure would be immediately recognized as presenting an exciting research opportunity, a product whose only asserted utility is as an object of such research is not patentable under 35 U.S.C. 101.

The specification puts forth that the polypeptides of the instant invention are specifically expressed in taste cells and that the polynucleotides could thus be used to generate taste topographic maps or to dissect taste transduction pathways (e.g. page 68-70). These proposed uses lack a substantial utility. Almost every polynucleotide and polypeptide has some tissue specific pattern of expression, and absent knowledge of any ligands to the disclosed polypeptides, or without some specific or particular guidance as to which "taste transduction pathway" the polypeptides are involved in, these uses are merely and invitation to perform further research into the properties of the disclosed polypeptides and polynucleotides or to try to find practical uses for them.

The specification puts forth that the polypeptide and/or polynucleotides could be used in forensic biology (page 69). While one of skill in the art would appreciate that polymorphisms in the disclosed sequences must exist in any large population, this amounts to nothing more than an invitation to the skilled artisan to try and find such polymorphisms. Moreover, the specification does not teach that any particular nucleic acid or amino acid sequence is distinctive of any individual nor of any particular phenotype, e.g. the specification does not assert that a mutation in the gene would effect the ability to perceive any particular bitter tastant – or bitter taste in general.

Thus, the instant application has failed to provide guidance as to how one of skill in the art could use the claimed invention in a way that constitutes a substantial utility. The proposed uses of the claimed invention are simply starting points for further research and investigation into potential practical uses of the claimed nucleic acids.

Claims 158-185 are also rejected under 35 U.S.C. § 112 first paragraph. Specifically, since the claimed invention is not supported by a substantial asserted utility, for the reasons set forth above, one skilled in the art would not know how to use the claimed invention so that it would operate as intended without undue experimentation.

Additionally, should a specific or otherwise substantial utility be established for claims 158-185, then claims 158, 159, 164-185 would be rejected under 35 U.S.C. § 112 first paragraph, because the specification does not enable any person skilled in the art to make and use the invention commensurate in scope with these claims. Claims 158, 159, 164-185 encompass polynucleotides encoding polypeptide variants of the polypeptide of SEQ ID NO: 8 i.e.

substitutions, deletions or insertions in a protein corresponding to SEQ ID NO: 8 or comprising only portions of SEQ ID NO: 8 Appellant has not provided sufficient guidance as to how to make and use the encoded polypeptides which are not 100% identical to the polypeptide of SEQ ID NO: 8, but which still retain a desired property of the polypeptide of SEQ ID NO: 8. The specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make. Furthermore, Appellant has not provided guidance as to what properties of the allelic variants or sequence variants of the protein corresponding to SEQ ID NO: 4 might be desired nor any guidance as to which amino acid substitutions, deletions or insertions to make to achieve any desired property. Appellant has not defined a difference in structure or difference in function between the protein corresponding to SEQ ID NO: 8 and variants of said protein. If a variant of the protein corresponding to SEQ ID NO: 8 is to have a structure and function similar to the protein corresponding to SEQ ID NO: 8, then the specification has failed to teach one of skill in the art which amino acid substitutions, deletions or insertions to make that will preserve the structure and function of the protein corresponding to SEQ ID NO: 8.

The specification has failed to provide an activity of SEQ ID NO: 8 to be used to evaluate the claimed variants for usefulness, e.g. no particular ligand has been disclosed to bind and activate the protein, so the artisan would not know how to test variants for functionality. The specification has not provided a working example of a usable variant of the polypeptide of SEQ ID NO: 8 nor sufficient guidance so as to enable one of skill in the art to make such a variant.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any

given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These regions can tolerate only relatively conservative substitutions or no substitutions (see Bowie et al., 1990, Science 247:1306-1310, especially p.1306, column 2, paragraph 2). However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Also, these or other regions may be critical determinants of antigenicity. It is well appreciated in the art of antibody production that it is unpredictable which amino acids are critical antigenic determinants (see Alexander et al., Proc. Natl. Acad. Sci. 89(3352-3356)1992. Protein antigenicity can be significantly reduced by substitution of even a single residue. Further, even if an amino acid substitution does not destroy the activity of the immunizing protein, the substitution may significantly reduce the antigenicity of the protein (see the Abstract of Alexander et al.). The specification does not provide sufficient guidance as to how to make antibodies that are specific to variants of SEQ ID NO: 8 that can be used for any specific purpose. The specification has not provided guidance as to natural variants that may exist, nor how to use antibodies specific to variants that might be created.

The problem of producing active variants appears especially difficult in the art of T2R receptors, to which the instant polypeptide is asserted to belong. The instant specification

appears to simply suggest to the artisan that art-recognized procedures for screening GPCRs (e.g. pages 50-63) are sufficient to identify functional variants of SEQ ID NO: 8 However, Hoon *et al., Cell* 96(541-551)1999, report that "We have attempted to determine the ligand/tastant specificity of TR1 and TR2 using a variety of strategies but have been hampered by the difficulty of functionally expressing these molecules in heterologous systems" see col 1 of page 547. Further, Chandrashekar et al. reported that they were able to record a response from only 1 of the 11 human T2R clones tested, see col 1 of page 707, and see above. Thus, the art regarding T2R receptors, as exemplified by Hoon et al., Chandrashekar et al, and Lindemann (discussed above), recognizes the complexity, unpredictability, and non-routine nature of the work involved in trying to assay functional T2R receptors. The instant specification has provided only general guidance to the skilled artisan -such guidance does not supply the artisan with the detailed methods one would need to possess in order to screen for functional variants. Further, the specification has offered no working example of such a screening method.

The specification has also failed to teach where to look for naturally occurring allelic variants of SEQ ID NO: 7, e.g. no disorder or phenotype has been asserted to correlate with a naturally occurring allelic variant, such that the artisan might now where to obtain a variant. The specification merely offers the skilled artisan the invitation to randomly try to find variants through trial and error sampling of animal populations.

Due to the large quantity of experimentation necessary to generate the infinite number of variant recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention,

the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function and the difficulties encountered in screening T2Rs, exemplified by Hoon et al., Chandrashekar et al., and Lindemann, and the breadth of the claims which fail to recite adequate structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope should a substantial utility be established for the claimed polynucleotides.

Claims 158, 159, 164-185 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification discloses a cDNA polynucleotide of SEQ ID NO: 7, yet the claims encompass polynucleotides not described in the specification, e.g. mutated sequences, allelic variants, or sequences that have a recited degree of identity. None of these sequences meet the written description provision of 35 U.S.C. 112, first paragraph. Although one of skill in the art would reasonably predict that these sequences exist, one would not be able make useful predictions as to the nucleotide positions or identities of those sequences based on the information disclosed in the specification.

The instant disclosure of a single polynucleotide, that of SEQ ID NO: 7, encoding a polypeptide with no instantly disclosed specific activities, does not adequately support the scope of the claimed genus, which encompasses a substantial variety of subgenera. A genus claim may be supported by a representative number of species as set forth in *Regents of the University of*

California v Eli Lilly & Co, 119F3d 1559, 1569, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997). A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus, or of a recitation of structural features common to the genus, which features constitute a substantial portion of the genus. The instant specification discloses, however, a single isolated polynucleotide sequence SEQ ID NO: 7, which is not sufficient to describe the essentially limitless genera encompassed by the claims.

The specification has not provided a particular essential feature, either a functional or structural feature, that the claimed genus of polynucleotides possess. The recitation of the property of hybridization does not, alone, provide sufficient information regarding the structure of the claimed polynucleotide variants. Further, most of these variants are expected to encode polypeptides having an amino acid sequence different than that of SEQ ID NO: 8 and thus having different structural and functional properties. Similarly, the recitation of a percent identity to SEQ ID NO: 8 provides no description of any amino acid sequence other that of SEQ ID NO: 8. The specification has not defined what particular common structural or functional properties are possessed by the claimed genus of polynucleotides. Thus one of skill in the art would appreciate that Appellant was not in possession of the claimed genus of polynucleotides at the time of filing.

The instant claims are not directed to that which is disclosed as essential to the invention, i.e. something that is homologous to the parent SEQ ID NO: 7 and has the function of the parent polynucleotide. Thus, with the exception of the of the polynucleotide of SEQ ID NO: 7, and other polynucleotides which encode a polypeptide of SEQ ID NO: 8, the skilled artisan cannot

envision encompassed variants. Therefore, only a polynucleotides encoding a polypeptide of SEQ ID NO: 8, and polynucleotides *consisting* of fragments thereof, or polynucleotides consisting of fragments thereof and heterologous sequences (e.g. carrier or tag sequences), but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph.

(11) Response to Argument

Beginning at page 11 of the Brief, Appellant argues that one of skill in the art would reasonably conclude that the claimed polynucleotide encodes a bitter taste receptor, and thus could use the polynucleotide to identify bitter ligands that specifically activate or modulate the activity of the encoded receptor and therefore modulate bitter taste transduction. This argument has been fully considered but not deemed persuasive. There are two separate issues that relate to these assertions as they regard support for a substantial utility. The first is the question as to whether or not a person skilled in the art would expect that the hT2R61 polypeptide is a bitter taste receptor. The second, and really the only important question is whether or not the knowledge that the polypeptide is a bitter taste receptor would provide for a substantial utility.

Regarding the first question, Chandrashekar and Adler provide the evidence that certain T2R members are, in fact, bitter tastant receptors. However, the state of the art, exemplified by Chandrashekar et al. and Adler et al., indicates that it was impossible to predict that a particular T2R would bind a bitter tastant. Chandrashekar tested 25 murine T2Rs and found only two that responded to a bitter ligand (mT2R-5 and mTR2-8). They also tested 11 human T2Rs and found

only one that responded to a bitter ligand. Thus, given any particular T2R, one could not be sure, or even more confident than not, that this particular T2R would bind a bitter ligand.

The second question is: does a general prediction that a T2R protein is a bitter ligand receptor, such general prediction later confirmed, provide an artisan with enough specific information to know how to use the T2R in such a way as to constitute a specific or otherwise substantial utility without subsequent research and experimentation into the properties of the T2R? Although the term "bitter taste receptor" appears to be a specific phrase, it is not. Instead, this phrase is thought in the art to encompass a verity of different receptors the study of which, in the words of (Perruccio and Kleinhaus, supra), "is especially complex because the structural diversity of the bitter molecules is the most varied of all other taste qualities". Applicant's assertion that the polypeptide could be used to search for the specific bitter molecule(s) that activate this receptor is simply an invitation to perform experimentation.

At page 11 of the Brief, Appellant lists a number of properties that the hT2R61 polypeptide has which would lend support to the idea that it is a bitter taste receptor. Among these are the properties of being encoded by an intronless gene, interaction with a G-protein and having a 7 transmembrane domain. This argument has been fully considered but not deemed persuasive. These properties are known in the art to common to most G-protein coupled receptors.

Appellant now argues that the specification discloses that the family of T2R members share an average of about 20-30% sequence identity of about at least 50 nucleotides in length. This argument has been fully considered but not deemed persuasive. One skilled in the art recognizes that these criteria are so broad as to be essentially meaningless. 50 nucleotides would

encode only 16 amino acids. Brenner et al. PNAS 95(6073-6078)1998 teach that one would need a stretch of about 150 amino acids sharing 30% identity just to be confident that the two proteins evolved from a common ancestor, and even this says nothing about whether the two share the same function, see col 2 of page 6067.

At pages 11-12 of the Brief, Appellant argues that the tissue distribution and chromosomal localization are consistent with the hT2R61 being a bitter taste receptor. Also at pages 12-14 the focus of Appellants arguments is on the expectation that the polypeptide is a bitter taste receptor. This argument has been fully considered but not deemed persuasive. The basis of the rejection is that calling the protein a bitter taste receptor does not provide the artisan sufficient knowledge to use the protein in another way than as a starting point to try to find what molecule(s) activate it. As set forth above, Chandrashekar tested 25 murine T2Rs and found only two that responded to a bitter ligand (mT2R-5 and mTR2-8). They also tested 11 human T2Rs and found only one that responded to a bitter ligand. Thus, from a practical stand point, given any particular T2R, one could not be sure, or even more confident than not, that this particular T2R would bind a bitter ligand. Additionally, Appellant argues that the examiner has provided no examples of a T2R which is non-functional. This argument has been fully considered but not deemed persuasive. From a practical stand point, the unresponsive T2Rs disclosed by Chandrashekar provide the examples of T2Rs that are nonfunctional.

At page 14 Appellant quotes the Adler reference, i.e., that they "presume that the high degree of variability between T2Rs reflects that need to recognize many structurally different ligands", and concludes that those skilled in the art would anticipate that the various members would be functional and bind different bitter ligands. This argument has been fully considered

but not deemed persuasive. First, the authors of Adler do not make any statement that this variability was limited to bitter ligands – only to structurally diverse ligands. Regardless, the point is that the specification simply invites the artisan to embark on a research plan to try to find the particular substances that bind to the protein among the "diverse universe of bitter substances", see line one of page 695 of Adler.

At pages 14-22, Appellant argues that subsequent experimentation by Appellant has proven that the polypeptide interacts with nitrosaccharin (a known bitter compound). This argument has been fully considered but not deemed persuasive. It is this type of research and experimentation that the instant specification invites the artisan to perform. Appellant now argues that the high through-put assay involving 15000 compounds, used by Appellant to discover the ligand for the polypeptide, is a more typical assay than that used by Chandrashekar wherein only a "small" (55) number of compounds were used, see page 19 of the Brief. This argument has been fully considered but not deemed persuasive. One skilled in the art appreciates that finding a ligand for an orphan GPCR using conventional or high-throughput techniques is a substantial research investment; and high through-put ligand discovery is far from routine - see Lahana R., Drug Discovery Today, 4(10)447-448, 1999 who answers the question "How many leads have we got from combinatorial chemistry and high-throughput screening so far?" – "none!", see the Title page; see also, Horrobin, DF, British Med. Journal, 322(7280)239, July 2003. The specification provides no particular high through-put library that could be used to routinely obtain compounds that interact with the instant protein.

At page 20 of the Brief, Appellant argues that one would not need to know that the polypeptide interacts with nitrosaccharin to use the polynucleotide. Appellant asserts that the

polynucleotide can be used as a probe to identify subjects who are potentially at risk for impaired ability to taste some bitter ligands. This argument has been fully considered but not deemed persuasive. This purposed use is simply an invitation to try to find mutants of the receptor and then to try to find any inability to taste a particular unknown bitter compound. Further, as discussed at length above, the invitation to use the polypeptide to search for agonists and antagonists is not a substantial utility but simply an invitation to perform further research and investigation.

At page 21, bridging 22 of the Brief, Appellant argues that the Chandrashekar reference provides compelling evidence that saccharin was considered to potentially be a T2R ligand, and because of this Appellant reasons that saccharin should be included in compound libraries to be screened for potential modulators of the polypeptide. This argument is not persuasive for three reasons. First, as set forth in the Advisory action, Chandrashekar use saccharin at a concentration wherein it acts as a sweet ligand, Appellant doesn't appear to challenge that assertion. Thus, the artisan would view the use of saccharin by Chandrashekar as an expectation that the protein might be a sweet receptor and not a bitter receptor. Second, Chandrashekar demonstrated that saccharin did not interact with any of the T2Rs tested so it is unclear why Appellant would conclude that "the teachings of Chandrashekar would reasonably suggest to a skilled artisan that saccharin desirably should be included in compound libraries to be screened for potential hT2R61 modulators...". To the contrary, one skilled in the art would not be inclined to use saccharin because of these negative results. Third, Appellant asserts that because saccharin was among the 55 compounds screened by Chandrashekar, then "the Chandrashekar reference provides compelling evidence that saccharin was considered to potentially be a T2R

ligand", see the last paragraph of page 21 to page 22 of the Brief. This assertion must be taken to mean that Chandrashekar viewed all of the 55 compounds tested as being potential ligands of the T2Rs, which is reasonable, yet these 55 compounds included sweet compounds, amino acids, and bitter compounds. Thus, Chandrashekar viewed sweet compounds, amino acids, as well as bitter compounds to be potential ligands for the T2Rs. This is in complete contradiction to Appellant's considerably lengthy arguments that the skilled artisan would expect from the teachings of Chandrashekar that all T2Rs are bitter taste receptors. This argument, however, does not have an important bearing as to whether or not the specification provides a substantial utility for the claimed polynucleotides, as discussed above.

Arguments relating to 35 USC 112, First Paragraph: Utility-Based Enablement Rejection

At page 22 of the Brief, Appellant asserts that claim 158 and dependent claims require the polynucleotide encode a "functional" bitter taste receptor. However, there is no mention of the word "functional" in the claim.

At page 22 bridging 23, Appellant argues that the because of the hybridization limitations and the percent identity limitations placed on the claims, the claimed genus of sequences encompassed by the claims is hardly essentially limitless. This argument has been fully considered but not deemed persuasive. The skilled artisan appreciates that from a practical stand point, the number of encompassed variants is essentially limitless, especially as there are no functional limitations in the claims.

At page 23 of the Brief, Appellant argues that one skilled in the art would understand from the teachings of the specification how to screen variant hT2R61 sequences to assess T2R

polypeptides that retain a desired function. This argument has been fully considered but not deemed persuasive. The skilled artisan would understand that he would have to discover what ligands activate the receptor before such screening processes could be begun, such ligands not being disclosed in the instant specification.

At page 23 of the Brief, Appellant now argues that the high degree of sequence identity of polypeptide encoded by the claimed polynucleotide sequences to the endogenous T2R61 would lead one to predict that a substantial number of these variant T2R61 nucleic acids would encode T2R61 variants that are likewise functional. This argument has been fully considered but not deemed persuasive. The claims encompass an astronomical number of artificially constructed variants of the naturally occurring T2R61; one skilled in the art would not view 95% identity as providing a reasonable proportion of functional variants, as now asserted by Appellant. The instant polypeptide (SEQ ID NO: 8) is disclosed as being 309 amino acids in length; thus a polypeptide having 95% identity with SEQ ID NO: 8 would have at least 15 amino acid substitutions relative to SEQ ID NO: 8. The skilled artisan appreciates that most of such polypeptides would not be expected to retain the functionality of SEQ ID NO: 8. Guo-HH et al. PNAS 101(25)9205-9210, 2004, recently reviewed the art and conducted an extensive study on the effect of amino acid substitution on the functionality of a wide variety of proteins and found that on average a single amino acid substitution had a 34% chance inactivating the functionality of the protein, see the Abstract. Thus, one skilled in the art the would not expect that a substantial number of variants that contained 15 amino acid substitutions would retain functionality, as now asserted by Appellant.

Citing case law, at pages 24-25 of the Brief, Appellant alleges that Appellant has asserted a specific and substantial utility in the specification which is supported by Dr. Zoller's declaration and later obtained experimental data; and that the examiner has failed to provide any evidence or objective reasoning to overcome the present patentable utility. This argument has been fully considered but not deemed persuasive. As set forth above, the invitation to conduct a research plan to use the claimed polynucleotide to try to discover a subject that has a defect in the ability to taste an unknown chemical is not a substantial utility. Also, as set forth above, an invitation to try to discover a ligand for the instant polypeptide is not a substantial utility. That Appellant has in fact subsequently succeeded in the discovery of the ligand, a ligand that was not even mentioned in the specification, does not merit the issuance of a patent. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson*, 148 U.S.P.Q. 689 (Sus. Ct, 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anti-cancer activity was alleged to be potentially useful as an anti-tumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 U.S.C. 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

> "The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is

> insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

As set forth above, the instant specification has not asserted a use that would be immediately useful to the public under the intended definition of useful as it appears in 35 USC 101.

At page 25 of the Brief, Appellant argues that, as the rejection under 35 USC 101 is improper, the corollary rejection under 35 USC 112, first paragraph is improper. This argument has been fully considered but not deemed persuasive, for the reasons discussed above.

At pages 25-26 of the Brief, Appellant essentially repeats previous arguments regarding enablement for polynucleotides encoding variants of hT2R61. These arguments have been fully considered but not deemed persuasive for the reasons discussed above.

Arguments Relating to 35 USC 112, First Paragraph, Written Description Rejection

At page 27-28 of the Brief, Appellant again asserts that claim 158 requires a functional bitter taste receptor, yet there is no such limitation in the claim. Appellant argues that the claims are of a determinate scope. However, this was not an issue regarding the basis of the rejections. The examiner maintains that from a practical stand point, the claims encompass an essentially limitless number of variants.

Appellant again argues that the claims provide both functional and structural limitations. This argument has been fully considered but not deemed persuasive. As set forth above, there is

no functional requirement in the claims. Second, the specification has not provided a particular essential feature, either a functional or structural feature, that the claimed genus of polynucleotides possess. The recitation of the property of hybridization does not, alone, provide sufficient information regarding the structure of the claimed polynucleotide variants. The property of hybridization is simply a cumulative effect of interactions between unspecified nucleotide positions. The property of hybridization provides no structural detail regarding the encoded polypeptide. Further, most of these variants are expected to encode polypeptides having an amino acid sequence different than that of SEQ ID NO: 8 and thus having different structural and functional properties. Similarly, the recitation of a percent identity to SEQ ID NO: 8 provides no description of any amino acid sequence other that of SEQ ID NO: 8. The specification has not defined what particular common structural or functional properties are possessed by the claimed genus of polynucleotides. Thus one of skill in the art would appreciate that Applicant was not in possession of the claimed genus of polynucleotides at the time of filing.

Applicant's assertions regarding a screen for variants have been fully considered but not deemed persuasive for the reasons discussed above.

Applicant's arguments at page 29 of the Brief regarding the use of saccharin in the Chandrashekar Paper have been fully considered but not deemed persuasive for the reasons discussed above. Addtionally, the examiner can find no mention of saccharin in the Alder paper. Applicant's additional arguments regarding case law and structural and functional features have been substantially addressed above and not deemed persuasive.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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Examiner
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MB

February 22, 2005

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